UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/124,485	07/29/1998	NICHOLAS MARK ANSTEY	73-97	6763

23713 7590 04/19/2005

GREENLEE WINNER AND SULLIVAN P C
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER	
CHEU, CHANGHWA J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/124,485	ANSTEY ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33,38,40,41,46 and 48* is/are pending in the application.

4a) Of the above claim(s) *27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40,41,46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and declarations filed on 2/16/2005 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claim 1-26, 34-37, 39, 42-45, 47 are cancelled.
2. Claim 48 is added to the instant application.
3. Currently, claims 38, 40-41, 46, 48 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of enablement

In vivo application

2. Claims 38, 40-41, 46, 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro, does not reasonably provide enablement for in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to apply the invention commensurate in scope with these claims.

The current case recites a method for the treatment of infection by a *Plasmodium* species in human, by administering an agent capable of increasing the level of nitric oxide in the body. The *Plasmodium* infected disease is particularly on malaria. Although applicant discloses general protocols in selecting patients, dietary control, sample collection, nitrate administering and measuring NO level, statistically analysis method, readjusting confounding factors, such as

renal failure. (See examples 1-21) The results in this instant application do not provide sufficient information or guidance to one ordinary skilled in the art to use or conduct the recited method in achieving the claimed effect.

Applicant provides data with respect to the inhibition of cytoaherence of infected RBC to C32 melanoma cells. (See Figure 1 and 2) The inhibition of cytoadherence has been shown "reduces the *likelihood* of infection of severe infection by Plasmodium species." (See page 14, last paragraph) Those data represent in vitro correlation between the different Plasodium strains (Figure 1) and the level of S-nitrosylation on RBC (Figure 2). Applicant asserts that the data support the notion that *RSNO treatment of parasitised red blood cells* inhibits cytoadherence to *C32 cells*. (See page 34, line 27-28) (emphasis added) This example merely shows an in vitro treatment on parasitised red blood cells, not an in vivo treatment on human subjects as recited in the current claim 38-39. There is no causal-effect relationship, i.e. decrease the severity of malaria disease. The data merely provides observation of the treatment on parasitised red blood cells with the RSNO.

The issue is that whether this in vitro model is an adequate model to reflect the effectiveness of an in vivo treatment on human. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area, the more specific enablement is necessary in order to satisfy the statutory requirement of 35 U.S.C §112, first paragraph. Applicant submits several review articles concerning the cytoadherence in vitro analysis (Note, ***after*** priority date; See below). In view of the current evidence, the instant cytoadherene in vitro assay does not support the notion of adequate correlation to the in vivo extrapolation.

It is noted that applicant use C32 melona cells which express CD36 molecules on the surface for cytoadherence assay for the infected red blood cells (See Figure 1 and 2). The CD36 molecule is the main endothelial surface protein bound to the infected red blood cells (See page 30, line 1-3). In the Cooke et al. reference (Parasitology Today 2000, Vol. 16, page 416), albeit the authors comment that "*cytoadherence is believed to be fundamental for the survival of Plasmodium faciparum in vivo, and uniquely, is a major determinant of the virulence of this*

parasite", that "*there are a number of aspects of this highly complex process that remain poorly understood*" (See Abstract)(emphasis added).

First of all, not all Plasmodium species require cytoadherence. For example, Plasmodium yoelii, a non-cytoadherent malaria parasite, can be just as virulent as the cytoadherent Plasmodium (See page 417, left column, third paragraph). Second, the CD36 adherence molecule, was lower in those people susceptible to severe malaria than individuals expressing normal levels of CD36. This is contrary to the in vitro data of cytoadherence (See page 418, left column, second-third paragraph). Particularly, Cooke et al. indicate that such evidence "*seem, in fact, to better argue against the role of cytoadherence in the causation of cerebral malaria (CM)" (emphasis added) Id.* Furthermore, another group of investigators, Newbold et al. (International J. Parasitology 1999 Vol. 29, page 927), also state that *"[a]t our current state of knowledge, strategies aimed at interfering with adhesion to CD36 dependent must be viewed with caution.*" (See page 934, right column, second paragraph) And, " *[a]s it seems that higher avidity binding to this receptor is associated with non-sever disease, abolishing CD36 dependent adhesion could lead to the selection in-vivo of parasites with affinity for a receptor which may lead to more virulent infection."* (emphasis added) *Id.* Therefore, there exists some concern(s) and controversy data for extrapolation the cytoadherence data, particularly the CD36 surface protein as used in applicant's in vitro assay, to adequately reflect the in vivo circumstance. Accordingly, under *In re Fisher* (aforementioned), the instant application contains more unpredictable area, it would deemed to require more specific enablement example or concrete data, in order to satisfy the statutory requirement of 35 U.S.C §112, first paragraph.

Administering Arginine in vivo

In addition, with respect to administering of arginine to the human subjects, applicant submitted his own post-filing date publication and argues that the claimed methods are applicable to the treatment of malaria disease (See page 7, first paragraph; See Exhibit I, *Anstey et al. Am. J. of Tropical Medicine and Hygiene (2002) 67(2): abst. 515*). In review of this publication, no data or results have been shown to the treatment of malaria by administering

agents to increase nitric oxide levels (emphasis added). The conclusion of this publication is that there exists an inverse relationship between Plasmodium malaria patients and the level of nitric oxide in the patients. Furthermore, another applicant's own post-filing date reference also implies uncertainty with respect to the treatment or prevention of the current purported method (See Exhibit A, The *LANCBT 2003 Vol. 361: 676*). Applicant states that "[w]hether or not severe disease is caused by, or results from, hypoargininsemia is *unclear*" (See page 677, right column, fourth paragraph)(emphasis added). Additionally, applicant concludes that "[c]linical trials are warranted to ascertain whether or not correction of L-arginine deficiency provides adjunctive prophylactic and therapeutic benefit to malaria" (See page 678, left column, last paragraph)(emphasis added). In another word, nearly 5- year after filing this application (filing date 7/9/1998), there is still some uncertainty concerning the in vivo effects, i.e. prevention and treatment.

Since no animal/or human were used as model system to treat Plasodium infected disease, it is not clear how reliable one skilled in the art may depend on the instant claimed method. The specification does not teach how to extrapolate data obtained from in vitro assays to the development of effective in vivo human treatment, commensurate in scope with the claimed invention.

Written Description

3. Claims 38, 40-41, 46, 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the instant invention, particularly the in vitro data of cytoadherence, is an adequate extrapolation of the in vivo situation. Particularly, examiner had pointed out the insufficiency of using the cytoadherence model (C32 melanoma cells expressing CD36 surface molecules) and the controversial data concerning of the cytoadherence in this Office Action. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 38, 40, 46, 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Rockett et al. (Infection Immunity 1991, Vol. 59, page 3280).

Rockett et al. teach a method of killing Plasmodium falciparum in vitro by nitric oxide derivatives (S-nitrosothiol), such as S-nitrosoglutathione or S-nitrocysteine (See Abstract and Table 2). The killing of Plasmodium would reduce or inhibit of its attach on the target red blood cells, thus diminish the pathological adherence of the parasitized red blood cells (See page 3281, right column, third paragraph). The inhibiting concentration on Plasmodium in vitro is 39.10 uM and 41.86 uM for S-nitrosoglutathione and S-nitrocysteine, respectively (See Table 2).

6. Claims 38, 40, 46, 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Stamler et al. (US 6153186).

Stamler et al. teach a method of treating the infected Plasmodium falciparum patient ex vivo by using the nitrothiol compounds, such as S-nitrocysteine, or S-nitroglutathione (See Col. 6, line 5-20; 26-39). The treatment is to reduce or ameliorate the abnormal parasitized red blood cell adheresion in vivo (Col. 5, line 32-40).

Response to Applicant's Arguments

7. Applicant's arguments concerning the C32 melanoma cell derived from human and the adequate in vitro phenomenon reflecting to in vivo are considered but are not persuasive in light of the reasons outlined as above.

8. Applicant further argues that the dosage administration ranges listed in the specification "meet[s] the law for obtaining a patent", and citing Scott v. Finney case law indicating that "[t]esting for the full safety and effectiveness of a prosthetic device is more properly left to the FDA" Applicant's arguments have been considered but are not persuasive. First of all, merely listing the possible ranges on drug/compound administration does not constitute sufficient evidence to enable one ordinary skill in the art as to practice the *unpredictable invention* as discussed above (emphasis added). Second, examiner is fully aware of the scope of executive institute (USPTO) in implementing patent law alone while not overstepping domains of other branch (FDA). Nevertheless, no issue of safety and effectiveness of the compounds has been

raised or discussed in the previous Office Action. Therefore, this issue is moot and no need of addressing.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

April 6, 2005

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
04/15/05